



# NICHD NEONATAL RESEARCH NETWORK

**How do I apply?**

# Origins of Neonatal Research Network (NRN)

- Neonatal management, especially for high-risk term and preterm infants, has often adopted practices without objective evaluation
- In an attempt to respond to the need for well-designed clinical trials in Neonatal Medicine, NICHD established the Neonatal Research Network in 1986

# Background NRN

- Collaborative participation with centers, data center and NICHD on common protocols
- Cooperative agreements
- Competitively peer reviewed
  - ◆ Open competition
  - ◆ Content of grant, concept proposal, depth of faculty and institution
  - ◆ Priority score
  - ◆ Diversity in population

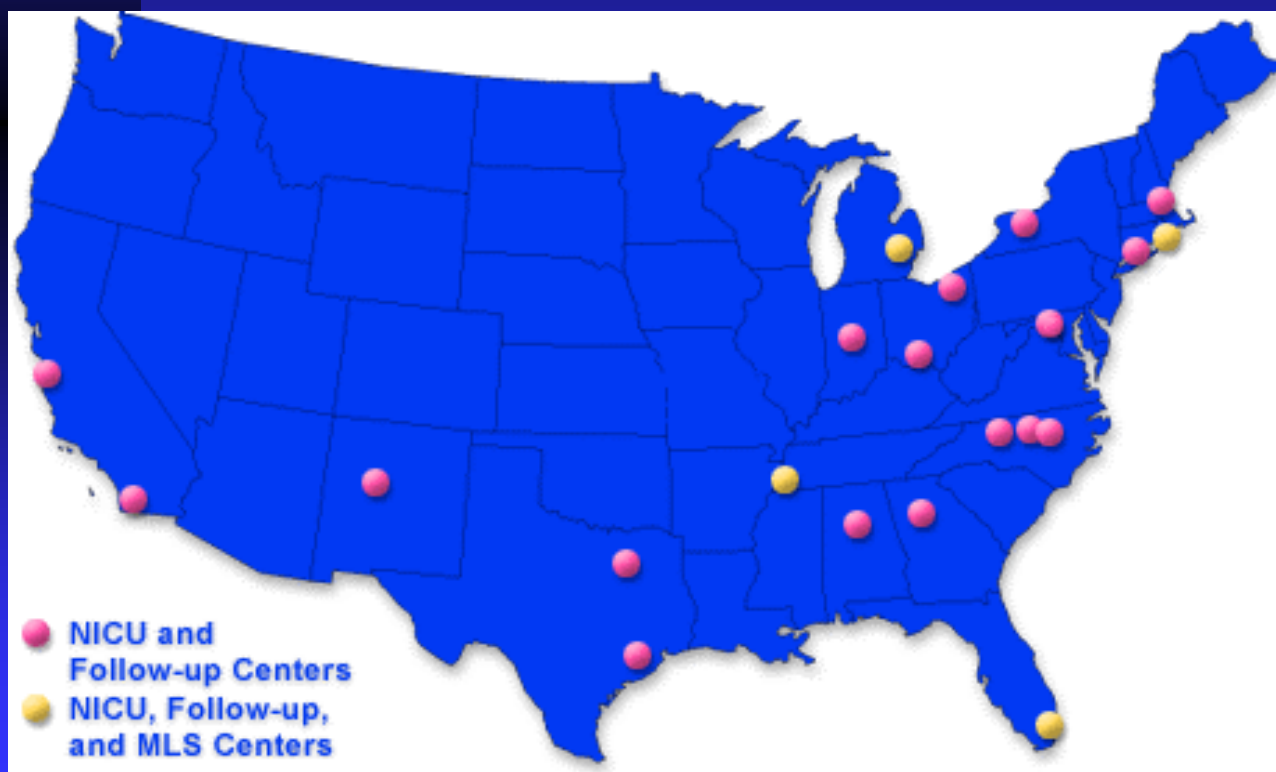
# NICHD NRN

## History

- 16<sup>th</sup> award year (beginning 4th cycle)
  - ◆ 1986 - 1991: 7 centers
  - ◆ 1991 - 1996: 12 centers
  - ◆ 1996 - 2001: 14 centers
  - ◆ 2001- 2006: 16 centers
- 20<sup>th</sup> year – 13-16 centers
- Data center
- Funding: NICHD; other Institutes and offices (NIDA, NHLBI, NEI): specific studies

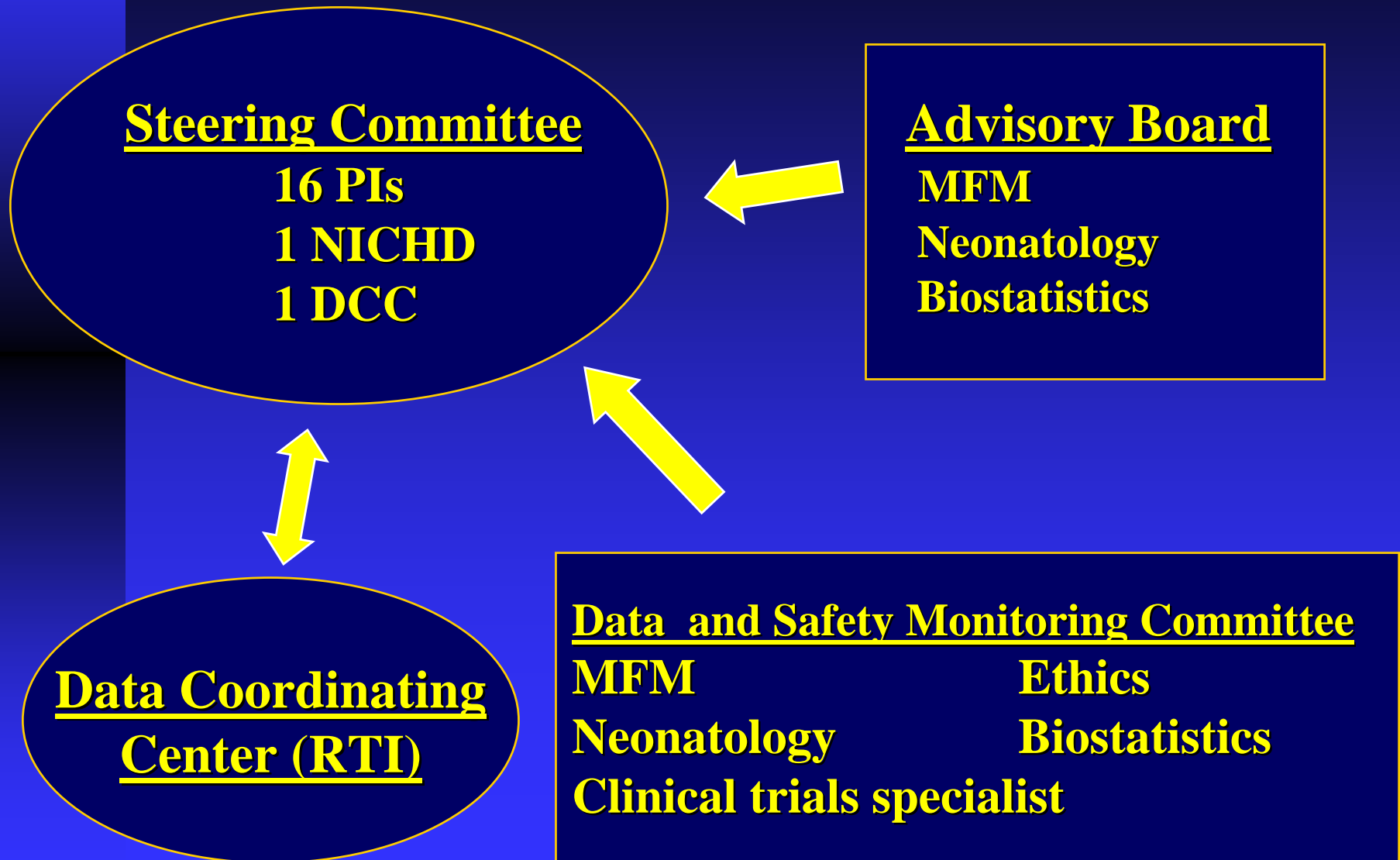
# ***NICHD NETWORK CENTERS 2001-2006***

- Data center
- 16 Clinical Sites
- NICHD
- > 60,000 admissions/yr
- Recompetition every 5 years



- Case Western Reserve University
- Univ. Texas – Southwestern
- Univ. Texas – Houston
- Wayne State
- Univ. Miami
- Emory
- Univ. Cincinnati
- Indiana Univ.
- Yale
- Brown
- Stanford
- Univ. Alabama
- Univ. Rochester
- Wake Forest
- Duke
- Univ. Cal. San Diego

# NRN Organization



# NICHD NRN Mission

The Neonatal Research Network is designed to conduct studies to investigate the safety and efficacy of treatment and management strategies to care for newborn infants.

# NICHD NRN Mission Aims

- Identify priority issues for research
- Evaluate interventions including efficacy, safety, and cost-effectiveness.
- Included: translational research, genetics, evaluation of new technologies in the promotion of infant health/prevention of disease

# NRN Committees

- Protocol specific committees
  - ◆ Each ongoing study/trial has a subcommittee
- Standing committees
  - ◆ Publications
  - ◆ Protocol Review
  - ◆ Concurrent Research
  - ◆ Generic Data Base
  - ◆ Data Access
  - ◆ Liaison
  - ◆ Genomics

# STEERING COMMITTEE

- Four SC meetings per year in DC metro area
- Meetings via teleconference as needed
- Composed of site PI's (Currently 16), DCC PI, and NICHD Program Scientist
- Works collaboratively

# NRN ONGOING TRIALS

- Observational Studies
  - ◆ Generic Data base
  - ◆ Follow up
  - ◆ aEEG
  - ◆ PCV-7
  - ◆ Candida
- Interventional studies
  - ◆ SUPPORT
  - ◆ Phototherapy
  - ◆ Inositol

# NRN: Personnel at each center

- Principal Investigator (PI)
- Alternate PI
- Follow Up PI
- Other investigators
- Research nurse coordinator
- Research nurses
- Data entry clerk

# SPECIAL REQUIREMENTS: ACADEMIC PRODUCTIVITY

- Prior or ongoing clinical trials (multi-center)
- Key contribution areas
  - ◆ Research development/design
  - ◆ Patient recruitment
  - ◆ Patient retention and study completion
  - ◆ Data collection and analysis
  - ◆ Publication track record

# **SPECIAL REQUIREMENTS:**

## **Neonatology Staffing**

- At least FOUR full time, neonatal-perinatal medicine board certified, academic physicians
- Complete description of staff qualifications (biosketch)
- Clinical, research, administrative, academic commitments
- Alternate PI
- If multiple sites – collaboration + publications

# **SPECIAL REQUIREMENTS: POPULATION FOR CLINICAL TRIALS**

- At least 500 admissions per year
- No more than 30% outborn
- Population specifics (births, NICU admission, transports, average daily census, length of stay, ventilation, ECMO, surgical cases)
- If more than one center, separate into columns
- Demographics, OB parameters, payment status

# **SPECIAL REQUIREMENTS: MATERNAL FETAL MEDICINE UNIT**

- MFMM service – high risk pregnancy and delivery
- MFMMU collaborator
- Maternal population (deliveries, C-sections, multiples, diabetes, hypertension)
- Consults performed by neonatal service
- MFMMU application – describe interaction

# SPECIAL REQUIREMENTS: CLINICAL CAPABILITIES

- Pediatric subspecialists
- Support staff- research coordinator, coverage for patient recruitment
- Pharmacy
- Respiratory therapy
- Current involvement in clinical trials

# **SPECIAL REQUIREMENTS: FOLLOW UP PROGRAM**

- Established neonatal follow up program
- Follow up rate – at least 80%
- 18-22 month FU
- Number of FU visits
- Designated facility

# **SPECIAL REQUIREMENTS: FOLLOW UP PROGRAM**

- Mechanisms for compliance
  - ◆ Maintaining family contact
  - ◆ Scheduling appointments
  - ◆ Actions for missed appointments
  - ◆ Home visits

# **SPECIAL REQUIREMENTS: FOLLOW UP PROGRAM**

- Designated FU PI (biosketch)
- Components of FU visit
  - ◆ Bayley Scales of Development II
  - ◆ Neurologic exam
  - ◆ Hearing assessments
  - ◆ Vision assessments

# Concept Proposal

- Hypothesis
- Specific Aims
- Background
- Methods
- Data Analysis

# PERINATAL DATA SYSTEM

- Description of electronic data system
- Recent application using data system

# RESEARCH STAFF

- Full time research coordinator
- Additional research staff
- Describe training, experience, qualifications and prior clinical trials experience

# Intent to Participate

- Clearly expressed intent to participate
- NRN projects given priority
- Expected to participate in all trials unless describe conflicts in application

## Departmental & Institutional Commitment

- Letters of support
- Evidence of past support
- Support: personnel management, space allocation, procurement, equipment, etc

# **SPECIAL REQUIREMENTS: STRENGTHS OF PI OR INSTITUTION**

- Special or Unique strengths
- State-of-the-art capabilities
- GCRC – document support
- Administrative strengths or experience
  - ◆ IRB
  - ◆ DSMC
  - ◆ Advisory Board for clinical research
  - ◆ Clinical research committees
  - ◆ Other strengths

# BASE BUDGET – COOPERATIVE AGREEMENT

- Principal Investigator – 10% effort
- Alternate PI, PI, or FU PI – up to additional 10% effort
- Research Coordinator 100% effort
- Data Entry Clerk – 50% effort
- Supplies/equipment – up to \$5,000
- Travel – 10 trips per year to DC metro area (4 for PI, at least 2 for coordinator, 4 – other)
- Other costs – up to \$3,000
- Base budget direct costs – limited to \$180,000

# CAPITATION

- Paid on per patient basis
- Study dependent
- Paid for enrollment (NOT screening)

# Receipt, review and start dates

- Letters of Intent Receipt Date(s): June 22, 2005
- Application Receipt Date(s): July 22, 2005
- Peer Review Date(s): Oct/Nov 2005
- Council Review Date(s): January 2006
- Earliest Anticipated Start Date: April 1, 2006

# Letter of Intent

- Descriptive title of proposed research
- Name, address, and telephone number of the Principal Investigator
- Names of other key personnel
- Participating institutions
- Number and title of this funding opportunity

Not required, not binding

# Sending application to NIH

- PHS 398 research grant application
- RFA label
- Signed, typewritten original + 3 signed copies
  - Center for Scientific Review
  - National Institutes of Health
  - 6701 Rockledge Drive, Room 1040, MSC 7710
  - Bethesda, MD 20892-7710
  - Bethesda, MD 20817 (express/courier service)
- Two copies
  - Robert Stretch, Ph.D.
  - Director, Division of Scientific Review
  - National Institute of Child Health and Human Development
  - 6100 Executive Boulevard, Room 5B01, MSC 7510
  - Bethesda, MD 20892-7510
  - Rockville, MD 20852 (express/courier service)

# Review and Selection Process

- Reviewed for completeness and responsiveness
- Evaluated for scientific and technical merit by peer review group
- Top half of applications discussed and given a priority score
- All receive written critique
- Second level of review by NACHHD Council

# Review Criteria: Qualifications and commitment of key personnel

- Scientific administrative, clinical and academic qualifications of PI and research team; qualifications of applicant institution
- Knowledge and experience in areas relevant to collaborative clinical research
- Commitment of staff time
- Experience and qualifications for data quality and management activities

# Review Criteria:

## Protocols and Procedures

- Quality of unit's participation in RCTs
- Willingness to work and cooperate with other NRN sites

## Facilities and Management

- Adequacy of administrative, clinical, data management facilities
- Institutional assurance
- Optional administrative strengths

# Review Criteria: Concept proposal

- Quality of proposed hypotheses, specific aim(s), background, methods, data analysis

## Review Criteria: Other

- Inclusion of minorities
- Plans for recruitment and retention
- Reasonableness of proposed budget
- Adequacy of protection for humans

# NRN ONGOING TRIALS

## ■ Observational Studies

- ◆ Generic Data Base
- ◆ Follow Up
- ◆ aEEG
- ◆ PCV-7
- ◆ Candida

## ■ Interventional studies

- ◆ SUPPORT
- ◆ Phototherapy
- ◆ Inositol

# GENERIC DATA BASE

- To provide baseline and outcome data for infants 401-1500 grams BW
- Prospective cohort study
- Admitted to NICU by day 14
- Baseline evaluation
- Outcome evaluation – pulmonary, cardiac, neurological, infection, GI, Hearing, ophthalmology, syndromes, growth, LOS, cause of death
- 36 week physiologic definition of BPD

# NRN Follow Up

- Follow up at 18-22 months corrected age of infants with birth weights 401-1000 grams
- Follow up rate  $> 80\%$
- Development assessed by Bayley exams
- Neurological exam
- FU PI's meet at PAS and at one steering committee meeting per year

# aEEG STUDY

- To determine if aEEG is a better predictor of clinical outcome following HIE than clinical exam at < 6 hours of age
- Currently recruiting

# PCV-7 Observational study

- *S. Pneumoniae* is a significant pathogen for which the pneumococcal vaccines is now available
- Little information in < 1500 gram infants
- To determine serologic titer against *S. pneumoniae* in VLBW infants undergoing vaccination

# PCV-7 Observational study

- Recruitment at the time of first vaccination
- 8 sites
- N = 200 with appropriate vaccine receipt and titer; aiming for 400, stratification by 100 gram birth weight increments from 401-1500 grams
- Began July 2004; 90 enrolled; 28 have completed the protocol

# Candida Observation Study

- Objective – to determine if new diagnostic tools (Beta glucan assay, PCR, D/L arabinotol ratios) are useful for early detection of candida and to develop a risk stratification model for predicting candida
- Began March 2004
- Enrollment criteria < 1000 grams birth weight with presentation for a sepsis workup
- N = 1750 infants with 100 positive for candida
- Currently, 418 enrolled with 23 positive for candida

# PHOTOTHERAPY STUDY

- To determine if aggressive versus conservative phototherapy results in difference in death or neurodevelopmental impairment
- Randomized, stratified, multicenter study
- 501-1000 grams
- Phototherapy intervention (bilirubin of 5 versus 8)

# PHOTOTHERAPY STUDY

- N = 1976, enrolled 1977 as of April 4, 2005
- Enrollment completed
- Null hypothesis – no difference in treatment
- Follow up in progress
- Anticipate results in mid-2007

# SUPPORT Trial

- To determine the effect of delivery room trial of positive end expiratory pressure versus intubation and surfactant and randomized pulse oximetry levels
- Randomized trial – 16 sites
- Gestational age 24 - 27 6/7 weeks
- Enrollment began 2/28/05
- NHLBI Co-Funding

# INOSITOL TRIAL

- To determine if supplemental 6-myo-inositol will decrease the incidence of severe ROP and death
- Secondary outcomes – BPD, long term FU
- Ross Abbot to provide drug
- NEI Co-funding

# INOSITOL TRIAL

- Several phases
  - ◆ Pilot to test random levels in infants
    - ◆ Being initiated at 7 sites
  - ◆ Single dose pK study
  - ◆ Multiple dose pK study
  - ◆ Large scale clinical trial

# Questions?

- Program: Rose Higgins MD
  - ◆ 301 4357909
  - ◆ [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)
- Grants Management Branch: Chris Robey
  - ◆ 301 435 6996
  - ◆ [robeyj@mail.nih.gov](mailto:robeyj@mail.nih.gov)
- Review: Bob Stretch PhD
  - ◆ 301 496 1485
  - ◆ [Stretchr@mail.nih.gov](mailto:Stretchr@mail.nih.gov)

<http://grants.nih.gov/grants/guide/rfa-files/index.html>